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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
LIU, SAMUEL W

ART UNIT	PAPER NUMBER
1653	13

DATE MAILED: 07/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/838,044	KASER ET AL.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *1-14,17,18 and 20-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15,16 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The response filed 19 May 2003 (Paper No. 11) as to cancellation of claims 26-39 and amendment of claim 15 have been entered.

Note that the grounds of objection and/or rejection not explicitly stated and/or set forth below are withdrawn; and note that the text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 101

Claims 15-16 and 19 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a well-established or disclosed specific and substantial credible utility.

The claimed protein is not supported by a specific asserted utility because the disclosed use of protein is generally applicable to screen a library of molecules, to purify a ligand from a sample (see page 4, the third paragraph) and thus is not a particular component of the pharmaceutical composition set forth in claim 9.

The specification sets forth use of the claimed protein (e.g., SEQ ID NO:6 polypeptide) for treating a disease state associated with the altered expression of gene in response to polycyclic aromatic hydrocarbon (PAH) exposure (see page 4, the second and the third paragraph). However, there is no working examples and guidance and no support as to how to make and use it in the specification regarding the claimed protein; the specification only provides evidence for human tissue expression at polynucleotide level NOT biologically active protein level. Thus, there is no specific utility associated with the claimed protein.

Also, the specification as filed does not disclose or provide any evidence that points to an activity (biological role or/and therapeutic role) of the protein. Additionally, there is no art of

record that discloses or suggests any activity for the claimed protein. Thereof, there is no substantial utility.

The specification sets forth antibodies and the fragments thereof that bind the claimed protein for diagnosing disease state characterized by over-or-under expression of the protein (see page 15, the forth paragraph). Such the recitation does not have positive input on the specific utility of the current disclosure because, at present, it has been widely accepted that the actual steady state level of mRNA molecules, is not well correlated with the actual protein abundance (see Aebersold, R. et al. (2000) *Annals of the New York Academy of Sciences* 919, 33-47), and because numerous proteins undergo are *up* or *down* cellular regulation upon the extracellular signals, *e.g.*, toxic PHA compounds. Since the current application only provides working example and guidance as to the altered gene expression at polynucleotide level in response to PAH toxic compound, which is not necessarily and sufficiently for supporting that the expressed protein level is proportional to the expressed polynucleotide level thereof, there is no specific and sensational utility or well-established utility associated with the antibodies and fragments thereof. After further search, a specific and substantial credible utility might be found for the claimed isolated compositions. This further characterization, however, is part of the act of the invention and until it has been undertaken, applicants' claimed invention is incomplete. The current disclosure is therefore deemed lack of specific and substantial utility or well-established utility.

Claims 15-16 and 19 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not

know how to use the claimed invention so that it would operate as intended without undue experimentation. This rejection stands for the reasons set forth in the foregoing statement of the grounds of rejection under 35 U.S.C. 101.

Applicant is not in possession of the claimed proteins and immunogenic fragments thereof for evidencing cytotoxicity or diagnosing the cytotoxicity associated disorder state in response to a PHA toxic compound. One of skill in the art would reasonably conclude that the disclosure insufficiently provides written description regarding the biological activity or role(s) of the claimed protein. The specification provide insufficient teaching, guidance, and no working examples as to how to make and use the protein in evidencing cytotoxicity in the exposure to PHA compounds, and diagnosing or/and treating a disease state associated with the exposure thereof.

Also, "an immunogenic fragment" (see claim 15) encompasses numerous polypeptide variants of the claimed protein (SEQ ID NO:6). One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of the variants to describe the immunogenic fragments. Thus, Applicant was not in possession of the pharmaceutical composition comprising the claimed protein and the claimed immunogenic fragment. *See University of California v. Eli Lilly and co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The current application is directed to a purified polypeptide that is used in a pharmaceutical composition in order to evaluating and identifying the environmental pollutants

and the pollutant-mediated disease or disorder states. However, the specification does not provide working example, teaching, direction or guidance as to chromatographic purification of the protein as claimed and use of the purified protein as a pharmaceutical composition in order to develop diagnostic and therapeutic agent for human condition, disease and disorders (see especially page 1, line 17-20, page2, lines 29-32 and page 4, lines 22-25).

Claim 15 sets forth a substantially purified protein which is expressed in response to exposure to cytotoxic benzo(a)pyrene, and an immunogenic fragment thereof derived from the disclosed protein sequence. Yet, applicants provide no factual evidence regarding the substantially purified protein (SEQ ID NO:6) and the purified protein-mediated or the protein-directed uses in therapeutics and diagnosis. Applicants predict the functional uses of the claimed protein based on inspection of the presence of the polynucleotide that encodes the interest protein in response to exposure to the PHA compound. Moreover, real protein sequence cannot be confirmed until the protein is isolated or purified.

The current disclosure sets forth an immunogenic fragment of the claimed protein. Yet, the specification provides no teachings, direction and working examples in regard to preparation of any fragments and testing for their immunogenity. The instant claim language "a immunogenic fragment" includes a large quantity of subsequences, i.e., variants (the number of the variants is estimated at least 1.7×10^5). Such the recitation does not require that the corresponding polypeptide possesses the full-length sequence set forth in SEQ ID NO:6; but rather encompasses any subsequences or have *per se* been. Neither the specification provides any working examples of any subsequences. Thus it would require undue experimentation of the skilled artisan to determine which subsequences of SEQ ID NO:6 would be selected for uses,

e.g., screening a library of molecules (see page 13, lines 23-28), raising antibodies for diagnostic assay, and formulating with pharmaceutical carrier for prognosis, prevention, and treatment of the PHA pollutant-mediated diseases and complications (see page 13, lines 21-22).

The make and use of the immunogenic fragments are thus unpredictable for the reason set forth *supra*. The use of the fragments for immunodetecting full-length protein of SEQ ID NO:6 produced by cells is therefore highly unpredictable as well. Note that the folded full-length protein is immnogenically different from the unfolded oligopeptide (e.g., immunogenic fragments). Characteristics of the surface of a folded protein play an important role in antibody recognition. The amino acids may be widely separated in the linear structure of the protein but are close together when folded. The epitope recognition by an antibody is of two basic types: (1) linear epitope that represents linear sequence of amino acids within oligopeptide or polypeptide, and (2) conformational epitopes in which the area recognized in the protein exists as a result of the 3-diamentional structure (*i*.e., folding structure) of the protein (see Miller, E. J. et al. *Am. J. Physiol.* (1991) 260, 1-12). Folding state and accessibility of antigen's idiotope to antibody are determining factors for affinity, specificity and valency with respect to antibody-antigen interaction.

The specification provides insufficient guidance as to (i) "conservative motif(s)" of the claimed protein for immunogenic recognition and (ii) applicability of fully folded, or partially folded, or unfolded protein including oligopeptide as a pharmaceutical composition. Since the claimed immunogenic fragments are structurally and functionally divergent in respect to their use in screening ligands and diagnosing and treating disorders associated with toxic compounds

e.g., benzo(a)pyrene *etc.*, the specification needs to provide sufficient guidance to support enabling.

On the other aspect, since pollutant PAH compound not only induces multiple polynucleotide expression (see the foregoing statement) but also exerts its cellar pharmacological effect through aryl hydrocarbon receptor/transcription factor (AhR) and induces apoptosis (see Shafat, A. *et al.* (2000) Mol. Pharmacology. 58, 515-525), these cellular characteristics of PHA would have an additionally unpredictable impact on the outcome of tissue expression profile as set forth in Table 1. In this regard, the specification needs also to provide sufficient guidance or direction to support the enablement.

Description of invention's reduction to practice, unaccompanied by any meaningful, distinguishing characteristics of evolved the peptide variants, i.e., immunogenic fragments, is insufficient to satisfy written description requirement of 35 U.S.C. §112, since inventors could have provided description of claimed oligopeptide or portion of SEQ ID NO:6 protein, since actual reduction to practice may demonstrate possession of embodiment of invention, but it does not necessarily describe what invention is, and since, in context of present case, disclosure of manner in which invention was reduced to practice does not satisfy more fundamental written description requirement set forth in Section 112.

In consideration of the issued stated *supra*, the amount and level of experimentation needed is undue.

Response to the rejection under 35 USC 101

The response filed 19 May 2003 argues that there is a reasonable possibility of the mRNA level indicating the expression level of the claimed protein of SEQ ID NO:6; thus,

applicants do not need to prove substantial utility but only "substantial likelihood" of utility, and asserts that a single reference (Aebersold et al.) does not constitute evidence of that actual steady state level of mRNA molecules is not well correlated with the actual protein (see page 8, the first paragraph). The applicants' argument is found not persuasive. The current application is directed to polypeptide, NOT polynucleotide (e.g., mRNA). The claimed polypeptide is theoretically predicted from a polynucleotide sequence (SEQ ID NO:1). In accordance with Aebersold et al. reference, the review article by Keene J. D. (*Proc. Natl. Acad. Sci.* (2001) 98, 7018-7024) also indicates that it is clear that the protein output of cells and tissues does not always correlate precisely with the mRNA content for a variety of reasons (see also the references incorporated: 21, 23, 30, 33, 54 and 55), and that, in particular, posttranscriptional regulation and posttranslational modifications can significantly affect the quality and quantity of protein that a given gene will generate (see he left column, page 7023). The current application is directed to the claimed polypeptide content and PAH-mediated cytotoxicity which is based on assaying the mRNA level of the polypetide. Thus, there is no specific and substantial utility associated with the claimed polypeptide.

The response asserts that the claimed polypeptide is useful as a tool for toxicology testing, drug development, and the diagnosis of disease, and argues the practical uses of the claimed invention in gene and protein expression monitoring, e.g., 2-D PAGE gels and Western blots (Furness Declaration at ¶ 11) and these uses are "well-established" (see pages 8-9, the first paragraph). It is noted that toxicology testing and drug discovery are not specifically recited in the specification as originally filed. Applicants argue that toxicology testing, e.g., evidencing genotoxic agent (e.g., PHA), is a well-established utility, and conclude that the claimed

polypeptides could be used in this manner and that the claimed invention thus possesses utility. However, for a utility to be "well-established " it must be specific, substantial and credible. In this case, as indicated at pages 8-11 of the response, that use of 2-D PAGE and Western blot analysis make a better assess for evidencing the PHA-mediated cytotoxicity. The particulars of toxicology testing with the polypeptide SEQ ID NO:6 are not disclosed in the instant specification. Neither the toxic substances that specifically induces expression alteration of SEQ ID NO:6 polypeptide nor the susceptible organ systems are identified. Because of this, such a utility is not specific and does not constitute a "well-established" utility.

In addition, since the specification does provide the working example as to the isolated SEQ ID NO:6 polypeptide or guidance as to isolation of the polypetide thereof, and since without isolated polypetide in hand, the antibody against the polypetide cannot be obtained, there is no established specific and substantial utility associate with immunogenic fragment of (see claim 15) the claimed polypetide. Further, potential diagnostic utility is not yet known and has not yet been disclosed. The utility is not substantial because it is not currently available in practical form. Moreover, in the specification, only data (see Table 6, column 7, row 1) showing % of the polynucleotide expressions of human tissues do not include the data of a control level of the expression thereof (i.e., non-exposure to PHA toxic compound). The data appear to be electronic Northern Blotting profile (note that Northern Blotting is a type of theoretical analysis) as which *is not specific* for SEQ ID NO:6. Thus, the working example of the current disclosure does not support specific utility as well as substantial utility. The artisan is therefore required to perform further experimentation on the claimed material itself in order to determine to what "use" any expression information regarding this amino acid sequence could be put.

With respect to the polynucleotide expression level related pharmaceutical use, the response alleges that the claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling (see page 11, section A, and pages 13-15). The applicants' argument is not persuasive. The first requirement for the use, e.g., drug development and disease diagnosis, is that one must know the biological significance of the polypeptide(s) which is/are being evaluated. And, the second requirement for the use is that the results of the profiling should be analyzable otherwise are useless because one would not know if the polynucleotide expression should be increased (up) or decreased (down) or even what significance could be attributed to such changes in expression profiles. Without knowing the up or down regulation, the skilled artisan cannot start out on developing a drug targeting on the expression level, or diagnosing a disease state based on evidencing expression level, absent evidence to the contrary. The specification provides insufficient teaching and guidance as to distinguishing the *differential* expression in certain tissue(s), i.e., *tissue-specific* gene expression upon exposure to toxic compound, e.g., PHA (see Table 1 which presents a very divergent tissue-expression pattern of SEQ ID NO:1 polynucleotide, i.e., from nervous tissue to reproductive tissue. Yet, there must be some expression pattern that would allow the claimed polypeptide to be used in a diagnostic manner. One needs to know, e.g., that the claimed polypeptide is either present only in a specific tissue in a disease state, to the exclusion of normal or is expressed in higher level in diseased tissue compared to normal tissue (i.e. overexpression). Evidence of a differential expression might serve as a basis for use of the claimed polypeptide as a diagnostic for a disease. However, in the absence of any evidence of relation of the claimed polypeptide to a particular disease or disorder

state, and of any correlation between the claimed polypeptide and any disease or disorder state or any known disease or disorder state, any information obtained from any expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole "utility" consists of its potential role as an object of use-testing" (*Brenner*, 148 USPQ at 696). The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

Additionally, the response argues that "the biological role or function of an expressed polypeptide is not required to demonstrate utility" (see pages 16-17). The applications' argument is unpersuasive. The current application is directed to the polypeptide SEQ ID NO:6, not polynucleotide. As stated above, no expressed polypeptide (SEQ ID NO:6) level has been identified to associate with response to the subject organism to pollutant, e.g., PAH. Thus, there is no specific and substantial utility associated with the claimed polypeptide. Moreover, even the mRNA level per se is analyzed through theoretical electronic Northern blotting. Because the specification does not presents evidence as to "+ 1" site where transcript starts via a real Northern-blotting experiment, there would be at least three open reading frames corresponding to three polypeptides starting from the three discrete methionine residues (see residues 1, 5 and 33) in the putative sequence SEQ ID NO:6. Thus, the skilled artisan would not be convinced to recognize a unique or/and novel polypetide induced by the response to PHA compound, and concludes that the current application lacks well-established utility.

Further, the response argues that the claimed polypeptide has numerous uses, e.g., in screening assays to identify specific ligand (see page 19, the second paragraph). The applicants' argument is not persuasive because (i) the claimed protein has not isolated in a physical form; (ii)

the claimed protein is theoretically deduced from a polynucleotide that in turn is obtained from theoretical electronic Northern blotting; thus, verification of the protein or/and the polynucleotide is necessary and a prerequisite for screening a specific ligand. The specification (page 23) sets firth a variety of ligands from DNA and RNA molecules, agonist, inhibitor, antibodies to drugs. Without knowledge of structural or/and functional characteristics of the claimed polypeptide, the skilled artisan will not be able to carry out the said identifying specific ligand. For instance, (i) identifying DNA-ligand requires knowing whether or not the protein containers zinc finger or leucine zipper or/and forms dimer etc.; (ii) without having the claimed protein in hand, the skilled artisan cannot perform specific binding assay for teasing an agonist; and (iii) without having known activity of a *non-inhibited* protein for a ligand or a substrate (as a control), the skilled artisan will not able to conduct any bioassay for identifying a *specific* inhibitor of the claimed protein. Therefore, the current invention lacks well-established utility.

Response to the rejection under 35 USC 112, the first paragraph

The response filed 19 May 2003 argues that use of LASERGEN software program for identifying suitable region of high immunogenicity, i.e., immunogenic fragment of the claimed protein (SEQ ID NO:6) helps reduce uncertainty in identifying suitable epitopes, and asserts that it would not require undue experimentation for the immunogenic fragment of SEQ ID NO:6 (see pages 23-24). Note that in order to satisfy the enablement set forth by 35 USC 112, the first paragraph, the invention has to teach how to make and use the claimed composition. The software only identifies an approach for evaluating or helping search for potential region of immunogenicity. Yet, this is not adequately correlated to the claimed protein variants. The

software has no positive impact on structuralizing the immunogenic composition or/and testing for immunogenicity of the composition thereof. The mediation of the immunogenic activity of the protein and fragments (variants, see the above-stated rejection) does not establish actual reduction to practice. In addition, the specification does not provide a representative working example or the related art in recorder in this regard so as to allow the stilled artisan to practice the claimed composition. Further, searching for the claimed immunogenic fragment of the protein requires undue experimentation (see the statement in the rejection *supra*). Identifying or/and characterizing a composition without teaching how to make and use the composition thereof is insufficient for enabling the disclosed composition. Thus, the applicants' argument is not found persuasive.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483. The examiner can normally be reached from 9:00 a.m. to 5:30 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703-308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

SWL

Samuel Wei Liu, Ph.D.

June 21, 2003

Karen Cochrane Carlson PhD

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER